

IN THE SPECIFICATION:

Please insert the following paragraph beginning at page 7, line 5 as follows:

The file of this patent contains at least one drawing executed in color as determined by the U.S. Patent and Trademark Office. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fees.

Please amend the paragraph beginning on page 7, line 15, as follows:

~~Figure 2 depicts~~Figures 2A-2B depict the nucleotide and amino acid sequences of rat OGFr. 5'- and 3'-untranslated regions are included. Repeats are denoted by single and double underlining.

Please amend the paragraph beginning on page 7, line 28, as follows:

~~Figure 4 depicts~~Figures 4A-4D depict the detection of six-day old (lane 1) and adult (lane 2) rat cerebellar nuclear proteins, native GST protein (lane 3), and recombinant GST-14e protein (lane 4) separated by SDS-PAGE and electrotransferred to nitrocellulose. A: Coomassie blue stained gel of the electrophoresed proteins. B-D: Western blots stained with polyclonal antibody generated against a 17-kD OGF binding protein (B), antibody made to fusion protein 14e (C), or antibody to GST (D). The staining patterns in panels B and C are similar. The blot in panel D demonstrates the specificity of the fusion protein antibody. The control antibody to GST detected GST and GST-fusion proteins, but not native nuclear homogenate. Arrows indicate the 62, 32, 30 and 17/16 kD OGF binding proteins.

Please amend the paragraph beginning on page 8, line 11, as follows:

~~Figure 5 depicts~~Figures 5A-5C depict distribution of OGFr in external germinal cells in adjacent midsagittal sections of 6-day old rat cerebellum (A, B) as detected by an antibody to the fusion protein 14e (A) or an antibody to the native 17-kD OGF binding protein (B). Internal

granule cells in adult rat cerebellar sections stained with antibody to the fusion protein (14e) (C) revealed no immunoreactivity. Arrows = immunoreactivity. Bar = 50 m.

Please amend the paragraph beginning on page 8, line 29, as follows:

~~Figure 7 depicts~~Figures 7A-7B depict representative saturation isotherm and Scatchard plot (inset) of specific binding of [³H]-[Met⁵]-enkephalin to a nuclear-enriched fraction of human placenta. A one-site model of binding was noted.

Please amend the paragraph beginning on page 9, line 3, as follows:

~~Figure 8A depicts~~Figures 8A-8B depict the nucleotide sequence (SEQ ID NO: 5) and the predicted amino acid sequence (SEQ ID NO: 6) of human OGFr, clone 8; 5'- and 3'- untranslated regions are included.

~~Figure 8B-8D depicts~~Figures 8C-8F depict alternatively spliced forms of OGFr. Colors indicate regions of identity between splice variants.

8B8C. Nucleotide splicing.

8C8D. Peptide structure of clones 1 and 127 compared to clone 8. Clone 1 and clone 127 lack the imperfect repeats.

8DE. Comparison of repeats in clones #4, 7, and 8. Differences in amino acids are noted in red (presumably due to polymorphisms in the population), and repeats are designated by alternate underlining. Repeats are numbered 1-5, and arrows indicate positions of apparent alternative splicing.

Figure 8E8F depicts FISH preparation and a companion ideogram (from the International System for Human Cytogenetic Nomenclature, 1995) showing the localization of OGFr to chromosome 20q13.3 (arrow).

Please amend the paragraph beginning on page 9, line 25, as follows:

~~Figure 9 depicts~~Figures 9A-9D depict Northern blot analysis of the receptor for OGF in human fetal (A) and adult (B) tissues, and cancer cells and tissues (C, D); corresponding β-actin level is shown below each blot.

Please amend the paragraph beginning on page 11, line 11, as follows:

Figure 16 depicts~~**Figures 16A-16B depict**~~ representative saturation isotherm of specific binding of [³H]-[Met⁵]-enkephalin to homogenates of PANC-1 nuclear protein. Mean ± SE binding affinity (K_d) and maximal binding capacity (B_{max}) values from 15 assays performed in duplicate. Representative Scatchard plot (inset) of specific binding of radiolabeled [Met⁵]-enkephalin to PANC-1 protein revealed a one-site model of binding.

Please amend the paragraph beginning on page 19, line 17, as follows:

The modification of an OGFr can include amino acid deletions, insertions, substitutions or truncations. It is appreciated by those skilled in the art that regions of OGFrs that are well conserved among species may be critical in preserving the biological activities of the OGFrs. Notably in this regard, a prominent feature shared by the isolated proteins of the present invention is the presence of multiple copies of imperfect repeats, as indicated in **Figure 2**~~**Figures 2A-2B and Figure 8**~~**Figures 8A-8F**. In addition, when comparing SEQ ID NO: 2 (rat OGFr) with SEQ ID NO: 6 (human OGFr) (**Figure 11**), a striking similarity is observed in the first 297 amino acids, with 87% being similar and 79% identical. Beyond this point, the number of both similar and identical amino acids drops notably. Thus, a 56% similarity and a 40% identical amino acid profile could be found from amino acids 297 to 464; a similarity ranging from 43 to 47%, and identical amino acids ranging from 20 to 23% were found thereafter. Therefore, rat OGFr and human OGFr have a great similarity at the N terminus, but dissimilarities at the C terminus.

Please amend the paragraph beginning on page 34, line 17, as follows:

Since the #14 clone was not full length, labeled #14 cDNA was used as a hybridization probe to screen the λgt11 fetal rat brain library for full-length clones. Thirteen positive clones

were identified and purified from the library by colony hybridization. Digestion of the purified clones with *EcoR*1 released a full size insert of 2.1 kb from clone #12. The #14 and the #12 cDNAs were sequenced in both directions. **Figure 2**Figures 2A-2B show the nucleotide sequence (SEQ ID NO: 1), and the deduced amino acid sequence (SEQ ID NO: 2), of the full length cDNA, #12; 5' and 3' untranslated regions have been included. The open reading frame was found to encode a protein of 580 amino acids, with 8 imperfect repeat units of 9 amino acids at positions 467 to 538. The molecular weight as calculated from the sequence is 58 kD. Search of the sequences in GenBank revealed no homology to this cDNA.

Please amend the paragraph beginning on page 38, line 4, as follows:

Antibodies to the recombinant fusion protein derived from clone #14 (14-GST) were titrated and 1:1000 dilutions detected 10 ng of fusion protein. When reacted with nuclear preparations of 6-day old cerebellum on a 1-dimensional Western blot, anti-14-GST recognized 5 polypeptides: 62, 32, 30, 17, and 16 kD, as well as the recombinant protein (**Figure 4**Figures 4A-4D). Western blots stained with antibodies generated against the native 32 kD binding protein detected the 62, 32, 30, 17, and 16 kD polypeptides, in addition to the recombinant protein (**Figure 4**Figures 4A-4D). The antibody to the recombinant fusion protein or the native 32 kD polypeptide stained homogenates of the adult rat cerebellum, but was of a notably lesser density than in the 6-day specimen (**Figure 4**Figures 4A-4D).

Please amend the paragraph beginning on page 38, line 31, as follows:

The staining pattern in immunocytochemical preparations employing antibodies to the recombinant fusion protein was similar to that observed when using antibodies to the authentic binding protein (**Figure 5**Figures 5A-5C). Both antibodies revealed immunoreactivity in the 6-day old rat cerebellum, with cells of the external germinal layer exhibiting prominent staining of the cytoplasm and low reactivity of the nucleoplasm. The internal granule cells of adult rat cerebellar tissues demonstrated little specific immunoreactivity with either antibody.

Please amend the paragraph beginning on page 42, line 20, as follows:

Binding assays were performed on human placenta using radiolabeled [Met^5]-enkephalin to characterize this tissue. Binding studies with human placenta and radiolabeled [Met^5]-enkephalin revealed specific and saturable binding, with a mean binding affinity (K_d) of $12.3 \pm 3.9 \text{ nM}$ and a binding capacity (B_{\max}) of $247 \pm 95 \text{ fmol/mg protein}$ (**Figure 7**Figures 7A-7B). A one-site model of binding was noted.

Please amend the paragraph beginning on page 46, line 8, as follows:

As shown in **Figure 9**Figures 9A-9D, in the human fetal tissues, transcript sizes of 1.7 and 2.4 kb were observed, whereas in the adult tissues and cancer cell lines and tissues only a 2.4 kb mRNA was detected. Receptor for OGF was of low abundance only in adult lung.

Please amend the paragraph beginning on page 52, line 4, as follows:

By use of the optimal conditions for protein concentration, time, temperature, and pH described above, in a buffer containing a cocktail of protease inhibitors, [^3H]-[Met^5]-enkephalin binding to PANC-1 nuclear homogenates (P1 fraction) was found to be specific and saturable (**Figure 16**Figures 16A-16B). Computer analysis of binding showed that the data best fit a one-site binding model with an average equilibrium dissociation constant (K_d) of $1.2 \pm 0.3 \text{ nM}$ and a mean maximal binding capacity (B_{\max}) of $36.4 \pm 4.1 \text{ fmol/mg protein}$. Nonspecific binding was calculated to be ~52% of the total binding.